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IN THE U.S. PATENT AND TRADEMARK OFFICE

43257

IN THE APPLICATION OF: CUTLER ET AL.

GROUP ART UNIT: 1616

SERIAL NO.: 10/003,465

EXAMINER: PRYOR

FILED: DECEMBER 6, 2001

FOR: METHOD OF CONTROLLING ZOOLOGICAL AND AQUATIC GROWTH

REQUEST FOR RECONSIDERATION

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

May 4, 2004

Dear Sir:

In response to the Nonfinal Action dated February 12, 2004 applicants respectfully request reconsideration of the rejection of claims 1, 2, 5, 7, 8, 16, and 18-24. These claims have been rejected as either anticipated or rendered obvious from the Stom paper. Applicants respectfully traverse.

Enclosed herewith is the Declaration of Horace G. Cutler, Ph. D. which is directed to the information and experiments reported in the Stom paper. As noted by Dr. Cutler in ¶2, the premise of the Stom paper was that quinones were formed as oxidation byproducts from exposure of plants to harmful polyphenols. Stom notes that these polyphenols are found in sewage pollutants, and his goal was to determine why sewage was harmful to such aqueous plants. (Stom in 1st paragraph)

Dr. Cutler points out, however, that Stom did not use benzoquinones in his study – he used dioxydiphenylsulfone derivatives. Without benefit of supporting information, Stom presumed that these derivatives would be indicative of activity. (Cutler decln. at ¶¶ 10-14) Stom also compounds the potential for confusion by later references to benzoquinone and dioxybenzene without noting that he was referring to the dioxydiphenylsulfone derivative. (Cutler decln. at ¶¶ 2, 9-11) It is believed that the author's reports of results with "benzoquinone" may have mislead the examiner and resulted in an inaccurate reading of the Stom teaching. The use of dioxydiphenylsulfone derivatives of benzoquinone neither anticipate the claimed invention nor, without some authoritative teaching that one skilled in the art would

accept as supporting the notion of equivalent expectations, would the use of such derivatives have rendered obvious the invention of the rejected claims.

Additionally, limited testing under controlled conditions of a derivative in a sample dish would not have been deemed sufficient by one skilled in this art to provide a reasonable expectation of success of the invention specified in the rejected claims. See, Cutler declaration at ¶¶ 3, 11.

Stom also did not perform tests on a target area infested with an aquatic pest using benzoquinones of the present claims. As mentioned above, Stom was trying to determine why sewage waters killed plants in discharge areas. Dr. Cutler observes that the plants actually tested with the benzoquinone derivative are leafy water plants (¶¶ 5-7) Presumably, these plants were desirable and were sought to be saved for if they were pests, Stom would applaud the effects of the sewage waters and seek to enhance their toxic effects rather than mitigate them. Such a method does not anticipate or render obvious the pest treatment method of the present claims.

The degradation to a benzoquinone that underlies the Stom tests also appears to be flawed. In Dr. Cutler's opinion, the likely structure of the dioxydiphenylsulfone derivative that was used in the Stom tests has "little chance that the material will degrade or be metabolized to a benzoquinone system." (Cutler decln. at ¶ 14) Such a fundamental flaw obviates any conclusion of anticipation or obviousness of the claimed invention based on the Stom paper.

Reconsideration and allowance are respectfully requested.

For the Applicants,

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DECLARATION OF HORACE G. CUTLER, PH.D.

I, Horace G. Cutler, hereby declare:

1. I am an inventor in the above-identified application for patent. I have reviewed the Stom reference, *mActa hydrochim. hydrobiol (5)* 291-298 (1977), and provide the following information and comments in connection with the rejections of the pending claims based on this reference.

2. The Stom paper addresses the premise that polyphenols are toxic to plants because quinones may be formed as oxidation products from plant exposure to polyphenols. The experiment used dioxydiphenylsulfone derivatives (quinones reacted with benzene sulfinic acid), rather than the quinones or benzoquinone due to benzoquinone lability and the stated tendency of the quinones to bind with functional groups of plant proteins. See, page 293, middle of the page. Thus, the paper reports on tests performed with sulfonated derivatives and postulates that these results are indicative of activity with quinones and benzoquinone. Later references in the paper to benzoquinone or dioxybenzene (e.g., p. 293) are, in my opinion, confusing as the tested compounds were actually sulfonated derivatives.

3. ~~Homogenized~~ HGC Plant tissues from *Nitella*, *Elodea*, and *Dunaliella* were used in the tests. There are no actual performance tests on any of the materials in a dynamic environment that would be faced by anyone trying to control a pest species population in a target area.

4. Considering Table 2, page 295, I note that none of the compounds shown is a quinone, with the exception of benzoquinone. These compounds are phenolics. Hydroquinone (old terminology) is a phenolic (cf. Merck Index, 11th edition, indent #4738).

5. I also note that *Elodea canadensis* is not an algae but, rather, a freshwater plant. Note the reference to "leaves of 10-15 nodes" on page 293, second paragraph. All algae are classified in the family *Chlorophyceae*. *E.*

canadensis is classified in the *Hydrocharitaceae* and, as such, it bears both staminate (male) and pistillate (female) flowers on separate plants. It is commonly known as Water Thyme. One skilled in this art would not find results with *Elodea canadensis* to be comparable to or suggestive of results on algae.

6. *Elodea canadensis* is an aqueous flowering plant, producing both staminate and pistillate flowers, is a member of the Hydrocharitaceae (and not in the same family as algae, which belong to the Chlorophyceae). It is also a rooting plant. Hence, none of the chemical data supplied in Table 2, relative to *Elodea*, is pertinent to the matter.

7. With respect to *Durtaliella*, all the compounds tested were phenolics. Such results are not indicative of possible results with benzoquinones. This leaves only the matter of *Nitella* to be clarified.

8. There is no recognized correlation of activity between materials used to kill algae populations and those used on flowering plants. One example is copper sulfate -- a compound used as an algaecide, but which is also used in flowering plants to maintain plant health. Copper sulfate has been used to kill algae in ponds (as a phytotoxin), but it is environmentally unsafe. Certain nefarious farmers still 'shock' their ponds with copper sulfate, but that practice raises issues not pertinent to the matters presented by this patent application. Copper sulfate has been used in conjunction with lime in viticulture as a mildewcide for over 100 years to control powdery mildew. It is also still used in New Zealand and, I suspect, in other countries, on apple trees and does not adversely affect the health of the apple tree or its fruit. Hence, copper sulfate can kill algae but does not have phytotoxic properties against flowering plants.

9. In the Stom reference, I note page 293, lines 29-30 which reads: "....To prove the appearance of quinone directly at the moment of formation, they were *transformed* with the aid of benzene sulfonic acid into *dioxydiphenylsulfones*." Note the statement diphenyl, meaning two phenyls. Thus, as the author next states, there was, "The necessity of working with stable derivatives, <u>but not the quinones themselves...</u>"

10. Therefore, the purported data in the Stom reference are predicated on results obtained with benzoquinone (and phenolic) <u>derivatives</u>, and not benzoquinone [note the singular use of the word] *per se*. And if, indeed, the parent compound was stabilized, then the parent compound

should induce effects very early in the experiment, and certainly quicker than the 15 minutes quoted, indicating that the derivative had to go through a biotransformation (¶ 11, below). Thus, my interpretation of the Stom paper, as one skilled in this art, is that these experiments suggest that the downstream compound (benzoquinone) is not active. If this compound had been active, the author would have demonstrated this in independent bioassays. The fact that the author did not substantiate this data, but rather used the dioxydiphenylsulfone derivatives to generate the data, illustrates that benzoquinone is not active in the bioassays.

11. I also note that in the Abstract, line 5, it is stated, "Formation of *o*- and *p*- benzoquinones *by the aquatic plants* (of the dioxydiphenylsulfones) implies that the dioxydiphenylsulfones are not active *per se* (i.e., the starting materials are bioinactive) but require biotransformation to become active. The details of this biotransformation do not specify of what and how, and what happens to the other phenyl group of the *derivatized* parent: is it, like many phenyl functions, an active antibiotic? The Stom reference cited by the examiner do not address or suggest the answers to these questions and would not, in my opinion, be accepted by those skilled in this art as establishing a reasonable motivation to arrive at the invention described and claimed in the patent application identified above.

12. The results shown in Table 1 and Table 2 assume the stated phenolics; *o*- and *p*- benzoquinone to be the active ingredients. Nowhere in the manuscript is a method given for direct analyses of these compounds. It is apparent to me that the author arrived at the presumptive bioactive concentrations of purported benzoquinone (<u>and their actual appearance was never proved analytically</u>) by applying a specific molar concentration of the dioxydiphenylsulfone *derivative* to be tested, noted the *apparent* speculated effect on SH groups, then subtracted the derivative moiety from the molar concentration employed and arrived at a theoretically derived figure.

13. There are no HPLC, mass spectrometry, or UV spectral data, or other analytical data to support the author's claims. The equipment was readily available in 1976-1977 when the work was conducted. Scientifically, the author cannot substantiate his/her claims based on the highly limited data presented.

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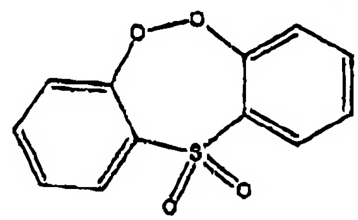
14. The structure of dioxydiphenylsulfone, which is the derivative the Strom paper (*Acta Hydrochim. Hydrobiol.* 5(3), 291-298, 1977) used in their assays, is presented below.



dioxydiphenylsulfone

15. After careful consideration of the chemical system, there is very little chance that the material will degrade or be metabolized to a benzoquinone system. Most likely, the epoxide will be broken open to yield a di-phenol, while the sulfone will be stable. If there is degradation of the sulfone it will not be converted to an –OH, which would be the next logical step if there is production of a benzoquinone. Further references to the metabolism of agents such as the dioxdiphenylsulfone may be found in Wilson and Gisvold, Textbook of Organic Medicinal and Pharmaceutical Chemistry, 11th Edition, J.H. Block, and J.M. Beale, Jr, Editors, Chapter 4: Metabolic Changes of Drugs and related Organic Compounds by S.J. Cutler and J.H. Block, Lippincott and Wilkins, Baltimore MD, 20004.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these were made with the knowledge that false statements made willfully are punishable by fine, imprisonment, or both a fine and imprisonment under Section 1001 of Title 18 of the United States; and further that false statements made willfully may jeopardize the validity of any patent issuing on an application in which the false statements were made.

30 April 04
Date

Horace G. Cutler